## REMARKS

Reconsideration is requested.

Claims 1-16, 21-22, 27-30, 32, 36 and 37 have been canceled without prejudice. Claims 17-20, 23-26, 31 and 33-35 are pending.

The Examiner is requested to contact the undersigned to arrange a personal interview at a time convenient for the Examiner and the Examiner's Supervisor which is prior to the Examiner mailing a further Action on the merits.

Claim 17 has been amended to obviate the Section 112, second paragraph, rejection of the same. Withdrawal of the rejection is requested.

The Section 103 rejection of claims 17-20, 23-26, 31 and 33-35 over Ogata (EP 1 197 225), Iwamura (Cancer, 1999, Vol. 86, No. 6, pages 1028-1034), and Burton (BBRC, 1990, Vol. 167, No. 3), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

The applicants submit, with due respect, that there is no motivation in the cited art to have combined the cited art to have made the claimed invention.

The claims provide a method for treating a kidney cancer comprising the administration to a subject of an effective dose of a PTHrP antagonist for inhibiting or decreasing tumor growth or a pharmaceutical composition containing it, said PTHrP antagonist being an anti-PTHrP antibody.

As recognized by the Examiner, Ogata et al fail to teach treating kidney cancer. See page 4 of the Office Action dated June 8, 2007.

Ogata teaches treatment of diseases caused by PTH or PTHrP. Ogata describes diseases caused by PTH or PTHrP as including

> "... a syndromes associated with malignancy caused by PTHrP (e.g. digestive system disorders such as diarrhea, vomiturition and nausea), proteometabolism abnormality (e.g. hyperalbuminemia) saccharometabolism, abnormality (e.g. reduction of glucose tolerance and reduction of insulin secretion), lipid metabolism abnormality (e.g. hyperlipidemia and reduction of serum lipoprotein lipase activity), anorexia, hematological abnormality (e.g. anemia, thrombosis and DIC syndrome), electrolyte abnormality (e.g. hyponatremia, hypokalemia and hypercalcemia), immunodeficiency (e.g. infection disease), pain, secondary hyperparathyroidism and primary hyperthyroidism which are caused by PTH, etc.
>
> Furthermore, the present invention provides an improving agent for the central nervous system disease caused by PTH or PTHrP, which comprises, as an active ingredient, an agonist or antagonist being to a PTH receptor or PTHrP receptor, or a substance binding to a ligand of the receptor to promote or inhibit binding between the ligand and the receptor. Examples of central nervous system diseases may include dyssomnia, neuropathy (e.g. schizophrenia, manic-depressive psychosis, neurosis and psychophysiologic disorder), nervous system (e.g. vomitation, nausea, mouth dryness, anorexia and vertigo), brain metabolism abnormality, cerebral circulation abnormality, autonomic imbalance, and endocrine system abnormality with which central nervous system is associated, etc." See page 3, ¶ [0016]-[0017] of Ogata.

Kidney cancer is not specifically recited or suggested in the detailed list of diseases described by Ogata.

The Examiner describes Example 4 of Ogata as relating to the administration of a humanized monoclonal anti-PTHrP antibody "to a rat cancer model". Id. The model of Example 4 of Ogata however involved implantation of human large cell lung carcinoma LC-6, to nude rats. The implanted lung carcinoma is described in Ogata as producing PTHrP which manifested in irregular autonomic movement in the untreated rats. Ogata teaches that administration of an anti-PTHrP monoclonal antibody

improved the effect of high PTHrP-related hypercalcemia on the central nervous system of the rats implanted with a human large cell lung carcinoma.

Burton et al. is understood to only concern studies carried out in vitro. The applicants believe that a person of ordinary skill in the art would not have expected an efficiency of an in vivo treatment on the basis of these in vitro results.

In addition, only one human renal cell carcinoma cell line has been used in the study such that the effectiveness of inhibitors of the PTHrP/RPTH1 system shown in vitro by Burton et al. on this unique cell line would not have led one of ordinary skill to have expected similar results with other human renal cell carcinoma cell lines or with tumors developing in vivo in animal models or in man.

Thus, the disclosure of Burton et al would not have led one of ordinary skill in the art to have expected, for example, the effectiveness of a treatment by anti-PTHrP antibodies on the growth of tumors of renal cell carcinoma established in vivo in the nude mouse.

This study goes back to 1990, and since, apart from work of the inventors, no other study had been carried out by these authors or other investigators to confirm or disprove these results.

Consequently, given doubts about the teaching of Burton et al relating to the effectiveness of an inhibitor of the PTHrP/RPTH1 system to treat a cancer of the kidney and the lack of incentive of Ogata et al. for the use of an anti-PTHrP antibody to treat another disease than a disease caused by PTHrP, the ordinarily skilled person would not have combined these two documents to make the claimed invention.

Finally, the Examiner is understood to rely on Iwamura et al to allegedly teach that elevated serum PTHrP has been detected in many renal cell carcinoma patients with hypercalcemia. However, Iwamura et al do not teach that kidney cancer is a disease caused by PTHrP for the following reasons.

Despite the high expression of PTHrP in RCC tissues, Iwamura et al rather makes apparent an inverse correlation between the PTHrP expression and the tumor recurrence in RCC patients. See Abstract : "*Tumor recurrence was significantly greater in the weakly or unstained group compared with the strongly stained group*" and "*The results of the current study indicate PTHrP(109-141) may be possible marker of cellular differentiation and may be useful for predicting recurrence free survival in RCC patients*"; p. 1031, right col., 1st ¶ : "*The strongly stained group had a significantly more favourable outcome*"; p. 1032, left col., end of 4th ¶ : "the expression of PTHrP(109-141) was noted to be correlated inversely with the recurrence rate of RCC (...). For tumors with greater staining, reccurence appeared to occur less frequently compared with tumors with little or no staining."

Furthermore, PTHrP has been predicted to likely be involved in growth inhibition and described to be a differentiation factor. See p. 1032, right col., 1st ¶ : "PTHrP may have fragments with growth inhibitory activity in the middle or carboxy-terminal regions. (...) it appears likely that PTHrP(109-141) may be involved in growth inhibition, most likely affecting differentiation of RCC. The inverse correlation of PTHrP(109-141) expression with the aggressiveness of RCC therefore is not surprising."; p. 1033, left col., 2nd ¶ : "Decreased expression of PTHrP(109-141) with increasing malignant

potential in RCC possibly may indicate a loss of the tumor cells' capacity to undergo differentiation."

Therefore, Iwamura et al rather teach that PTHrP has an antitumoral role and teach away from the claimed invention. It can be reasonably deduced from the cited reference that PTHrP inhibition will contribute to the tumor development in RCC.

Contrary to the teachings of Iwamura et al, the present specification demonstrates that antibodies directed against PTHrP (independent of the targeted region, N-terminal, intermediate or C-terminal) decrease the proliferation of tumor cells (see Fig 4, 6 and 8).

The combination of cited art fails to teach or suggest the claimed invention. Moreover, Iwamura et al teach away from the claimed invention and demonstrate that the claimed invention would not have been obvious.

Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

The Examiner is requested to contact the undersigned to arrange a personal interview at a time convenient for the Examiner and the Examiner's Supervisor which is prior to the Examiner mailing a further Action on the merits.

Respectfully submitted,

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